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ORIGINAL ARTICLE

Small vessel disease and clinical outcomes after endovascular treatment in acute ischemic stroke

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Abstract

Background Pre-existing small vessel disease (SVD) has been associated with poor functional outcomes in patients with acute ischemic stroke treated with intravenous thrombolysis; however, there are scarce data in patients treated with endovascular therapy. We aimed to investigate the associations between SVD and clinical outcomes in patients treated with endovascular therapy.

Methods We retrospectivel y evaluated patients with acute ischemic stroke in the anterior circulation receiving endovascular treatment. We assessed SVD markers with visual scales using non-contrast computed tomography. Early outcomes included intracerebral hemorrhage and 7-day/discharge stroke severity, and late outcomes included modified Rankin scale (mRS) 90 days after stroke. We used logistic and ordinal regression models adjusted for age, sex, stroke severity, and time-to-groin puncture time.

Results A total of 175 patients were included in the study, mean (±SD) age 72.3 (± 12.4) years, 90 (51%) males. Among SVD features, only brain atrophy was associated with 7-day stroke severity (OR = 2.28; 95% CI = 1.11–4.68) and with worse mRS at 90 days (OR = 2.72; 95% CI = 1.25–5.91). Global SVD burden was associated with worse mRS at 90 days (OR = 1.63; 95% CI = 1.01–2.62) but not with 7-day stroke severity (OR = 1.71; 95% CI = 0.97–3.01).

Conclusions Pre-existing SVD burden, mainly driven by brain atrophy, negatively affects early and late clinical outcomes in anterior circulation ischemic stroke treated with endovascular therapy. Our results may help prognostic stratification of stroke patients treated with endovascular therapy.

Keywords Small vessel disease · CT · Endovascular treatment · Acute stroke · Clinical outcomes

Introduction

Small vessel disease (SVD) is a pathology that affects microcirculation of the brain, and is a major cause of stroke and dementia worldwide. Although small vessels' abnormalities are not detectable with current imaging techniques, magnetic resonance imaging (MRI) and computed tomography (CT) can reveal SVD effects on the brain. SVD has a heterogeneous imaging phenotype, ranging from microhemorrhage to brain atrophy [1]. MRI is currently the gold standard for in vivo evaluation of SVD; however, useful information can also be gathered with non-contrast CT scan (CT), routinely used in acute stroke setting for assessment of patients suitable for acute stroke therapy. Pre-existing SVD has been linked to poor outcomes after stroke after intravenous thrombolysis [2]; however, few studies investigated whether small vessel disease affects clinical outcome after endovascular treatment, and the majority of them used old-generation devices [3, 4]. Furthermore, such studies focused mainly on a single SVD feature (e.g., white matter changes), whereas a growing body of evidence suggests that global SVD assessment may provide more precise information about effects of the pathology on the brain [5–7].

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With data from a clinical series, we aimed to investigate the associations between single SVD features, total SVD burden, and clinical early and late outcomes after endovascular treatment with new-generation devices in patients with acute ischemic stroke due to large vessel occlusion in the anterior circulation.

Methods

Patients

We retrospectively analyzed consecutive clinical data of patients admitted at a single University Hospital with acute ischemic stroke due to occlusion of a large vessel in the anterior circulation treated with endovascular treatment, according to current evidence-based treatment. Variables of interest included age, sex, baseline stroke severity assessed with National Institutes of Health Stroke Scale (NIHSS), onset to treatment time (OTT), and cardiovascular risk factors. Each patient received neurological examination and NIHSS by a stroke neurologist. Multimodal CT imaging (CT, multiphase CT angiography [CTA] of the cervical and intracranial vessels and CT perfusion [CTP] before any treatment) was performed. Patients with inclusion criteria for recombinant tissue plasminogen activator (rt-PA) administration were treated accordingly, otherwise were treated only with primary endovascular treatment. Patients underwent endovascular treatment if they had (1) Alberta Stroke Programme Early CT score (ASPECTS) from 6 to 10 [8], (2) moderate-to-good collaterals on the multiphase CT angiography (CTA) [9], and (3) ischemic penumbra/infarct core mismatch larger than 50% of the total hypoperfused area identified by visual inspection on CT perfusion maps. Moderate-to-good collateral circulation was defined as the filling of 50% or more of the middle cerebral artery pial arterial circulation [10]; mean-transit-time (MTT) lesion represented total hypoperfusion (i.e., ischemic penumbra), cerebral blood volume (CBV) lesion indicated infarct core, and ischemic penumbra was defined as the mismatch between MTT and CBV lesions [11]. Each patient received a CT scan 24 h after the acute treatment and a 3-month outpatient clinic visit. We did not exclude from endovascular treatment patients with time-from-symptoms-onset unknown, but evaluated each case on the basis of clinical history and neuroradiological findings. The present study was conducted following the tenants of the Declaration of Helsinki. Informed consent was obtained from each patient where possible. Whether the patient was unable to give informed consent but was eligible to treatment, the treatment was performed prior agreement between the stroke neurologist and the neurointerventionist, as per usual practice in such emergencies, and collected afterwards. We excluded from treatment patients who refused endovascular procedure.

SVD and angiographic assessment

Two independent reviewers (FA, GDT), blinded to demographic and clinical characteristics, rated SVD features on pre-treatment plain CT scan (i.e., leukoaraiosis, lacunes, and cerebral atrophy) following STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) criteria [1]. Where early ischemic changes were too large to reliably grade SVD, evaluation of SVD features was made on the non-ischemic hemisphere. We performed a preliminary intraclass correlation coefficient (ICC) between the two reviewers on 40 CT scans. We separately graded leukoaraiosis severity in anterior (score 0–2) and posterior (score 0–2) with Van Swieten Scale (VSS) [12], obtaining a 5-point scale. We defined lacunes as round or ovoidal hypodense lesions ≤ 20 mm of diameter in basal ganglia, white matter and/or brainstem. We evaluated cortical and central cerebral atrophy with a 3-point scale (0 = "none," 1 = "moderate," and 2 = "severe") against a reference template and summed the single scores to obtain a 5-point scale for evaluation of global cerebral atrophy [2].

To evaluate global SVD, we assigned 1 point for each of the following if present: severe lucencies (VSS ≥ 3) in anterior or posterior periventricular white matter, lacunes ≥ 2 (multilacunar state), and presence (≥ 3) of cerebral atrophy. The combined 4-point ordinal score assessed the global burden of SVD ranging from 0 (no imaging features of severe SVD) to 3 (presence of each SVD feature graded as severe) [13]. The score has been previously tested in relation to blood-brain barrier permeability [5], white matter perfusion [14], and clinical outcomes [13].

The intraclass correlation coefficient for single SVD features between the two readers was as follows: lacunes 0.80 (95% CI = 0.64–0.89), central atrophy 0.88 (95% CI = 0.79–0.93), cortical atrophy 0.75 (95% CI = 0.56–0.89), leukoaraiosis 0.99 (95% CI = 0.98–0.99). In case of uncertainty, the grading was performed by consensus.

Vessel occlusion site was defined on angiography findings. Recanalization was assessed with the thrombolysis in cerebral infarction (TICI) scale [15] at the end of the endovascular procedure. We indicated good recanalization as TICI 2b/3.

Outcomes

We investigated the following early outcomes: (1) any intracerebral hemorrhage 24 h after endovascular treatment according to the ECASS II criteria [16] and (2) 7-day/discharge (in case of patients discharged before 7 days) NIHSS score by quartiles as early functional outcome [17]. As late functional outcome, we evaluated modified Rankin scale (mRS) score 90 days after the index stroke as follows: 0–1 = excellent outcome, 2–3 = good outcome, 4–5 = bad outcome, 6 = death.

Statistical analysis

We described general characteristics of the population with summary statistics and used ANOVA, Mann-Whitney *U* test, and Pearson χ^2 as appropriate, to test differences among groups. We evaluated associations between single SVD features and outcomes, and then we tested associations between the SVD score and outcomes using logistic and ordinal regression for binary and ordinal outcomes, respectively. We retained in multivariate analysis explanatory variables with $p < 0.1$ and adjusted for age, sex, NIHSS, and onset-to-treatment (onset-to-groin puncture) time. We considered statistically significant a p value< 0.05. Statistical analysis was carried out using SPSS for Windows (version 23.0; SPSS, Armonk NY, IBM Corp.).

Results

From January 2015 to May 2017, 200 patients underwent endovascular treatment. In seven patients, brain imaging was not available for evaluation, 18 (9%) had occlusion in the posterior circulation and were excluded from the final analysis. This left 175 patients with occlusion in the anterior circulation (Fig. 1) and CT available for SVD assessment.

Mean (±SD) age was 72.3 (± 12.4) years; 90 (51%) patients were male. Median NIHSS (IQR) was 20 (15–24); median (IQR) onset-to-groin puncture was 255 (210–330) minutes; 98 (57%) patients received intravenous thrombolysis before endovascular treatment (Table 1). Pre-stroke mRS was 0 in 134 (77%) patients, 1 in 19 (11%), and 2 in 10 (6%). Nine (5%) patients were treated out of protocol with a pre-stroke mRS of 3; three (2%) patients had missing pre-stroke mRS. Five (2%) patients have had a previous non-disabling stroke. A total of 89 (51%) patients had proximal middle cerebral artery occlusion (M1), 16 (9%) had carotid occlusion, 26 (15%) distal middle cerebral artery occlusion (M2), and 44 (25%) carotid-middle cerebral artery (tandem) occlusion. Endovascular treatment alone was performed in 98 (56%) patients, 75 (43%) patients received rt-PA and endovascular treatment, and 2 (1%) patients had treatment data missing.

Patients with SVD features were older ($p < 0.001$) and had more frequently vascular risk factors (hypertension and coronary artery disease; $p = 0.025$ and $p = 0.008$, respectively) compared to patients without SVD. A total of 28 (16%) patients had severe leukoaraiosis, 49 (29%) had severe brain atrophy, and 37 (21%) had one or more lacunar infarcts but only 9 (2%) had two or more lacunar infarcts (Fig. 2). SVD score distribution across the population is showed in Fig. 3.

A total of 124 (71%) patients had good recanalization (TICI = 2b/3) at the end of the endovascular treatment. Regarding early outcomes, 40 (23%) patients had cerebral hemorrhage of any grade according to ECASS II criteria; there were no differences between patients with or without SVD (26% vs 22%, respectively; $p = 0.494$). Severe leukoaraiosis (OR = 1.17; 95% CI = 0.55–2.89) and the presence of two or more lacunar infarcts (OR = 1.69; 95% CI = 0.49–5.85) were not associated with the NIHSS score at 7 days, whereas severe brain atrophy was associated with 7-day NIHSS score after adjustment for confounders (OR = 2.28; 95% CI = 1.11–4.68) (Fig. 4a). In ordinal multivariable analysis, global SVD score was not associated with 7-day NIHSS score (OR = 1.49; 95% CI = 0.93–2.38) although a clear trend towards worse NIHSS was present (Fig. 4b). At 3 months, a total of 32 (18%) patients had died. Severe leukoaraiosis (OR = 1.44; 95% CI = 0.67–3.11) and two or more lacunar infarcts (OR = 1.65; 95% CI = 0.39–6.92) were not associated with functional outcome at 3 months, whereas severe brain atrophy more than double increase the odds to have unfavorable functional outcome in ordinal shift analysis (OR = 2.72; 95 CI = 1.25–5.91) (Fig. 4a). SVD total score was associated with worse mRS at 3 months in ordinal shift analysis (OR = 2.72; 95% CI = 1.25–5.91) (Fig. 4b). After adjustment for confounders, in ordinal shift analysis, we observed a negative effect of brain atrophy on 7-day NIHSS score (OR = 3.05; 95% CI = 1.19–7.76) and 3-month functional outcome (OR = 2.44; 95% CI = 1.01–5.88), and confirmed the trend towards a negative effect of SVD score on 7-day NIHSS score (OR = 1.71; 95% CI = 0.97–3.01) and 3-month functional outcome (OR = 1.75; 95% CI = 0.99–3.08).

Discussion

In patients with anterior circulation stroke treated with endovascular treatment, we found an unfavorable effect of pre-existing SVD, driven by brain atrophy, on early and late functional outcomes. We did not observe any relation between pre-existing SVD and cerebral hemorrhage at 24 h.

Sporadic cerebral SVD is the commonest type of SVD [18] and may be considered as a composite product of aging and vascular risk factors on the small vessels of the brain. In vivo investigation of cerebral small vessels is challenging; however, we can visualize and measure the effects of the diseased microvasculature on the brain parenchyma. SVD has been associated with hemorrhagic transformation and worse outcomes after intravenous thrombolysis [2, 5, 19], suggesting that SVD may exert negative effects on outcome after stroke, increasing the harm of intravenous rt-PA and reducing its efficacy on reducing disability. Our results translate this paradigm also to patients treated with endovascular treatment. Few studies specifically addressed whether SVD may influence outcomes after endovascular treatment. Three studies with old-generation devices reported a higher occurrence of hemorrhagic transformation in patients with leukoaraiosis and a worse functional outcome at 3 months [3, 4, 20]. Conversely,

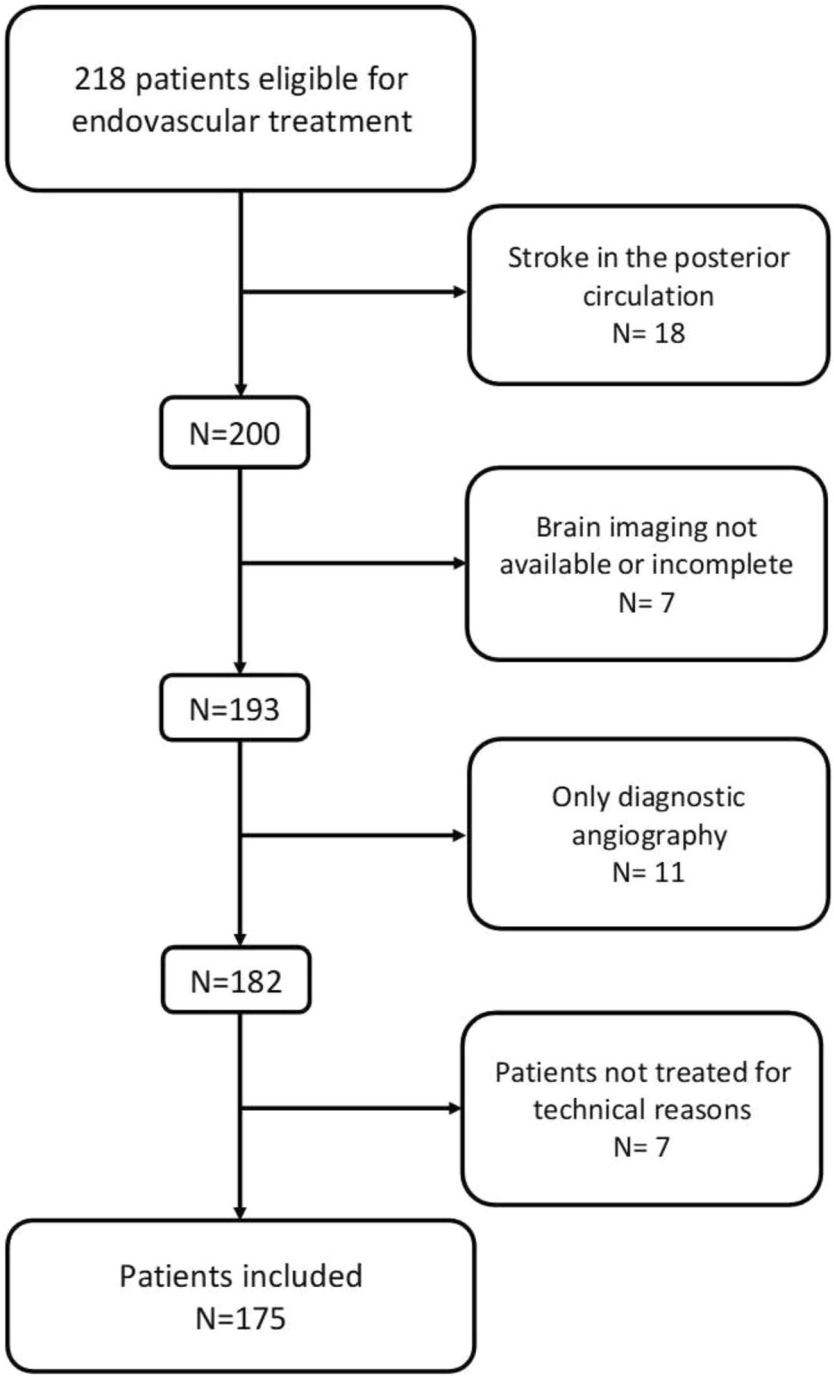

Fig. 1 Flow diagram of study population

we did not observe any relationship between leukoaraiosis and hemorrhagic transformation nor clinical outcome. This may be partly due to the use of new-generation devices, in keeping with a recent study that reported no effect of white matter changes, on functional outcomes after stroke [21].

Differently to previous studies that found a negative effect of lacunes [19] and pre-existing infarcts [2] on stroke outcome treated with intravenous thrombolysis, we found that the presence and number of pre-existing lacunes were not associated with early and late clinical outcomes. However, we point out that the number of lacunes, leukoaraiosis, and brain atrophy in our study was considerably lower compared to those of the aforementioned studies, perhaps reflecting the selection process of eligible candidates for endovascular treatment compared to the more indulgent criteria for rt-PA. As a consequence, our study may have been underpowered to detect meaningful association between SVD features and hemorrhage or between SVD burden and 7 days NIHSS. Nonetheless, we found that pre-existing brain atrophy was associated with worse early and late clinical outcomes. To our knowledge, this

Table 1 Baseline characteristics of study population

	Total $N = 175$	SVD		p value
		Absence (SVD score = 0, $N = 113$	Presence (SVD score 1 or 2, $N = 62$	
Age, mean ± SD	72.3 ± 12	*68.6 ± 13*	*79 ± 8*	*< 0.001*
Gender, male	90 (51.4)	59 (52)	31 (50)	0.779
NIHSS, median (IQR)	20 (15–24)	20 (15–25)	20 (17–24)	0.297
Time-to-groin, minutes, median (IQR)	255 (210–330)	250 (210–333)	268 (225–303)	0.832
Procedure length, median, minutes (IQR)	62 (38–95)	66 (38–106)	61 (39–92)	0.947
Hypertension[Ø]	95 (57)	*55 (51)*	*40 (69)*	*0.025*
Atrial fibrillation[Ø]	49 (30)	30 (28)	19 (33)	0.502
Coronary artery disease[Ø]	33 (20)	*15 (14)*	*18 (31)*	*0.008*
Diabetes[Ø]	14 (8)	8 (7)	6 (10)	0.516
Hypercholesterolemia[Ø]	28 (17)	18 (17)	10 (17)	0.925
Aspirin[Ø]	38 (22)	20 (18)	18 (29)	0.082
Smoke[Ø]	20 (12)	*17 (16)*	*3 (5)*	*0.046*
TICI 2b/3	124 (71)	85 (75)	41 (66)	0.189

Values are number (%) or median (IQR). *SVD* small vessel disease, *SD* standard deviation, *IQR* interquartile range, *NIHSS* National Institutes of Health Stroke Scale; *Ø* = 9 missing data. Italics values were those with statistical significance <0.05

association has not been previously investigated in stroke patients treated with endovascular therapy. Similarly to our findings, a pre-specified analysis from the Third International Stroke study (IST-3) found that pre-existing brain atrophy was independently associated with unfavorable outcome 6 months after ischemic stroke treated with intravenous thrombolysis [2]. Brain atrophy is common in elderly and may result from degeneration of connection fibers consequent to white matter changes and lacunar infarct, with consequent thinning of the cortex. It has been included among imaging markers of SVD [1, 22], but is also a common finding in primary neurodegeneration [23]. Other authors assessed global vascular and neurodegeneration features on the brain and described the Brain Health Index, an automated measurement of the global health of the brain [24]. We acknowledge that the association we found may be due to a neurodegenerative process rather than SVD itself. However, this supports that a pre-existing status of brain frailty, detected and rated with simple imaging techniques, and expressed as a radiological surrogate (single SVD features and global SVD burden), may negatively affect outcomes of acute stroke therapy. This may have implications to target selection criteria for future clinical trials on acute stroke therapy, since we could expect a diluted effect of a putative therapy on patients with pre-existing high burden of SVD. We investigated the whole spectrum of SVD features as seen with CT scan, following the concept that total SVD burden may allow more accurate estimate of size effects on clinical outcomes than single SVD features. To support this, the total SVD burden score showed a dose-effect response, reinforcing the validity of the findings.

Remarkably, in the subgroup of patients who achieved good recanalization (i.e., successful endovascular treatment), brain atrophy and SVD had a larger magnitude of effect than in the whole study population. Such findings are in keeping with another study that identified leukoaraiosis as a predictor of futile recanalization after endovascular treatment [25]. An analysis of three neutral randomized controlled trials of patients treated with endovascular therapy showed that age, higher NIHSS, and delayed endovascular treatment were associated with worse clinical outcome despite successful vessel recanalization [26]. However, our results suggest that pre-existing characteristics of the brain, such as atrophy and global SVD, negatively affected early and late clinical outcomes independently from age, NIHSS, and time to treatment. Despite mean age was higher in the group of patients without SVD, we found that multivariable analysis demonstrated an independent effect of brain atrophy and SVD on clinical outcomes. This suggests that detectable and measurable brain features may provide more relevant information compared to important than anagraphical age with regard to relevant clinical outcomes, focusing on individual characteristics. The reasons underlying the disappointing outcomes of endovascular treatment in patients with high SVD burden may vary from reduction of the blood flow [14, 27] to impaired neural connectivity [28] and may translate in worse outcomes. Pre-existing SVD burden, revealed by leukoaraiosis, lacunes, and brain atrophy with plain CT scan, may act as a surrogate of age and vascular risk factors, and reliably provide prognostic information. In this view, SVD seems to play a detrimental role in mitigating the beneficial effects of recanalization of the occluded vessel, which is the

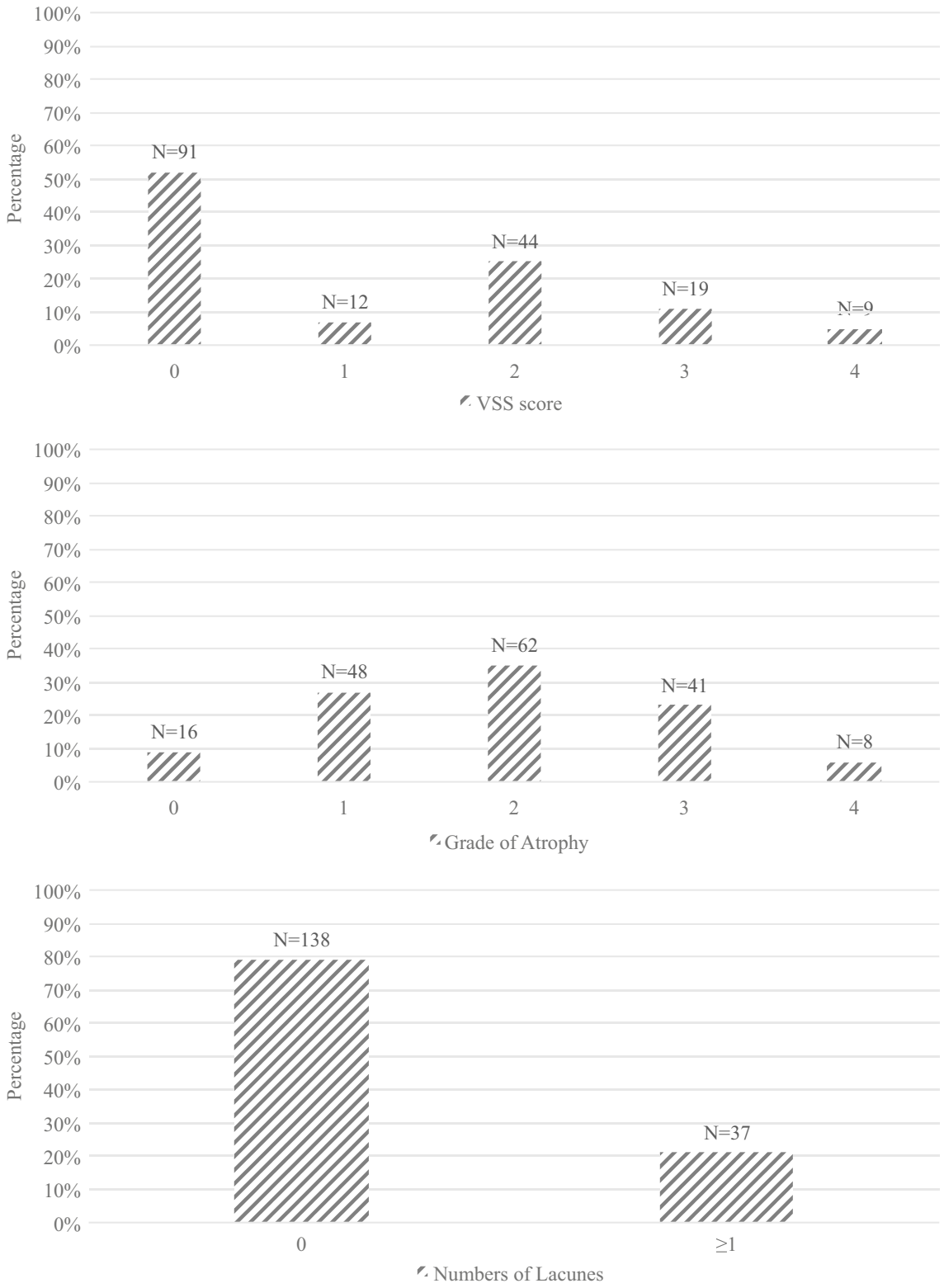

Fig. 2 Distribution of single small vessel disease features in study population

target of endovascular therapy and one of the most powerful predictors of clinical outcome [29]. We underscore that SVD is not a contraindication to endovascular treatment. Patients may still benefit from endovascular therapy; however, our result informs that one could expect marginal magnitude of effect in those with higher SVD burden and brain atrophy.

We acknowledge limits to our study. As a retrospective analysis of a clinical series, we lack a group of controls (i.e., patients

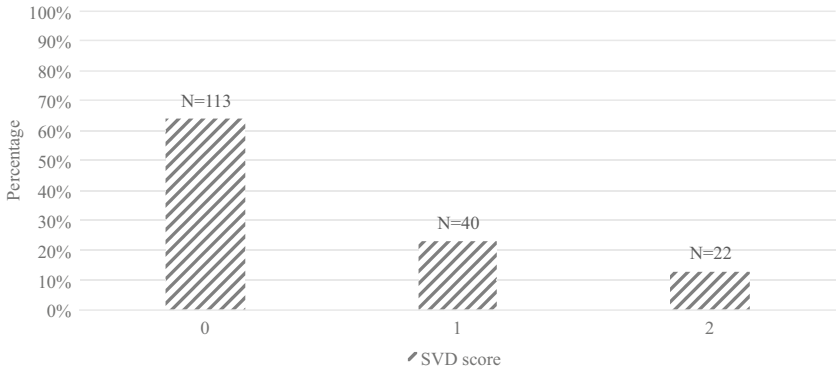

Fig. 3 Distribution of SVD score in study population

not treated with acute stroke therapy), our results should be therefore interpreted with caution and are not targeted to change clinical practice. Rather, our study is hypothesis generating, and external validation with appropriate study design and targeted population is required. Furthermore, the small sample size we analyzed may result in underpowered results to accurately estimate size effects. In fact, we point out that we found less SVD features in our population compared to previous studies, possibly reflecting the selection of patients eligible for endovascular treatment. However, our study population has comparable size to previous studies. We selected patients eligible for endovascular treatment in the anterior circulation according to current guidelines; however, we included also off-label treated patients, according to the choice of the treating physicians. Although this could have introduced heterogeneity in the study population, the single-center data collection allowed standardization of clinical and instrumental procedures, thus limiting the selection bias. Finally, we assessed SVD with CT scan, whereas the gold standard for in vivo assessment of SVD is MRI. We are aware that MRI is more sensitive in detecting the whole spectrum of SVD features, and that some imaging features, such as giant perivascular spaces, may be difficult to distinguish from lacunes only with CT scan. This might add imprecision to measurements and estimation of SVD in the acute phase of stroke. However, we used scales validated for both CT and MRI for grading of SVD [2, 12]. Although MRI allows a more sensitive detection of SVD, it is not widely available for acute stroke assessment and may have contraindications, whereas the

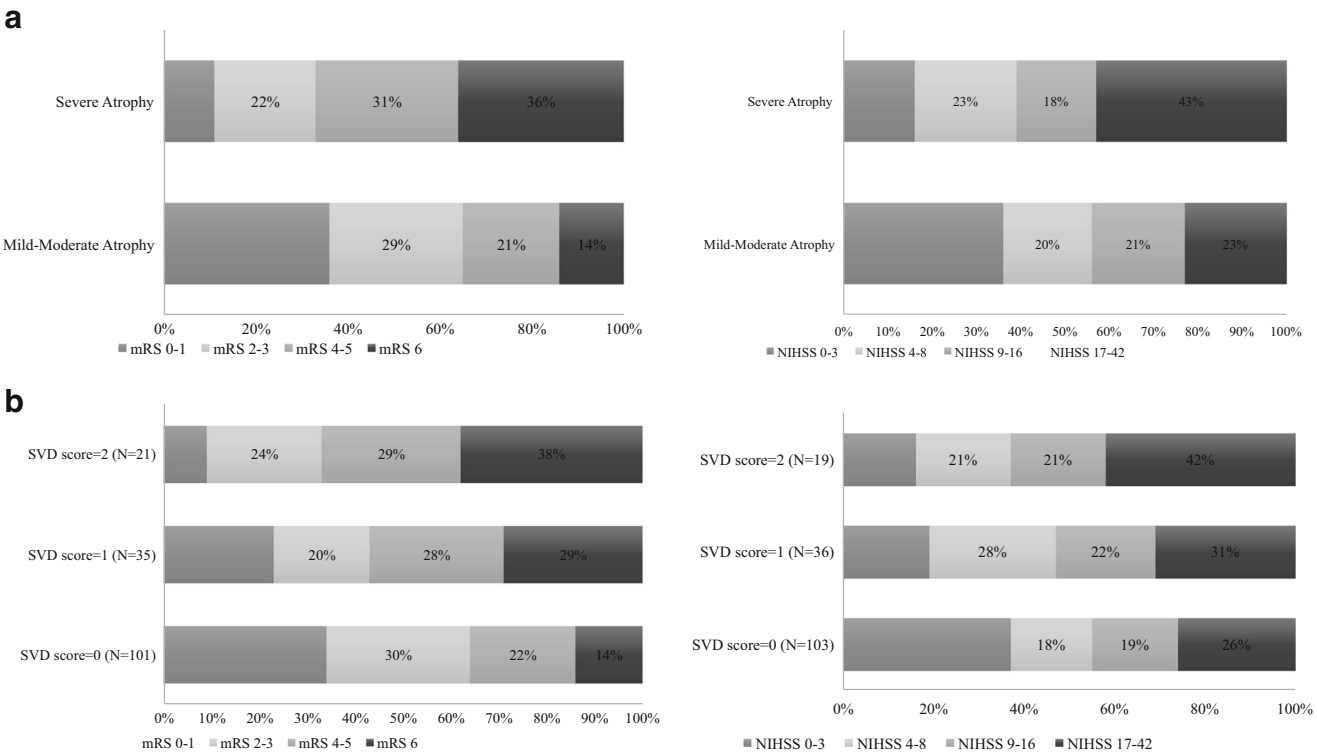

Fig. 4 Crude rates of the effect of severe brain atrophy (**a**) and SVD score (**b**) on categorized 7-day NIHSS score and mRS at 3 months. Odds ratios are from ordinal analysis adjusted for age, sex, NIHSS score, and onset-to-groin puncture time

qualitative scales we adopted using CT could be implemented in clinical routine. We acknowledge that the SVD score requires further validation in other cohorts and cross-validation with MRI but represent an attempt to quantify the effect of global SVD burden on the brain, and has been already tested in previous studies [5, 13, 14].

In conclusion, in ischemic stroke patients treated with endovascular therapy, pre-existing SVD, mainly driven by the presence and severity of brain atrophy, is associated with worse early and late clinical outcomes, but not with occurrence of hemorrhagic transformation. Measuring SVD before acute stroke treatment may help prognostic stratification of patients eligible for endovascular therapy and help design of future clinical trials. Our results suggest that the presence and measure of SVD should be a research focus in future revascularization studies.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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